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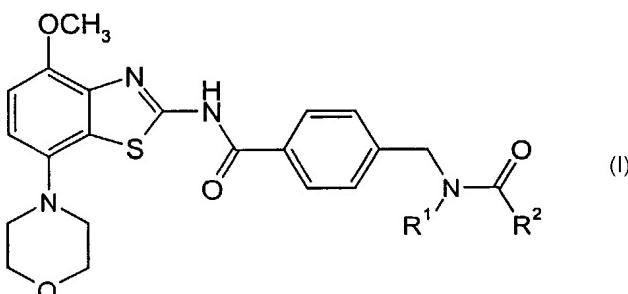
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(54) Title: BENZOTHIAZOLE DERIVATIVES

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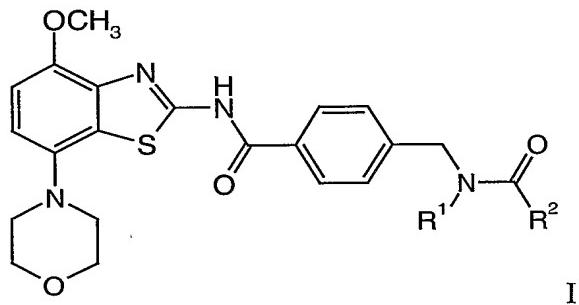


(57) Abstract: The present invention relates to compounds of the general formula (I) wherein R¹ is hydrogen or lower alkyl; R² is lower alkyl, -(CH₂)_n-O-lower alkyl, -C₃₋₆-cycloalkyl or -(CH₂)_n-NR'₂; R' is hydrogen, lower alkyl or -(CH₂)_n-O-lower alkyl, independently from each other for R'₂, or R'₂ may form together with the N atom a pyrrolidine ring; n is 1, 2 or 3; and to pharmaceutically acceptable acid addition salts thereof. It has surprisingly been found that the compounds of general formula I are adenosine receptor ligands. Specifically, the compounds of the present invention have a good affinity to the A_{2A}-receptor and they are therefore useful in the treatment of diseases, related to this receptor.

Case 21018

Benzothiazole derivatives

The present invention relates to compounds of the general formula



wherein

- 5 R¹ is hydrogen or lower alkyl;
- R² is lower alkyl, -(CH₂)_n-O-lower alkyl, -C₃₋₆-cycloalkyl or -(CH₂)_n-NR'₂;
- R' is hydrogen, lower alkyl or -(CH₂)_n-O-lower alkyl, independently from each other
for R'₂, or R'₂ may form together with the N atom a pyrrolidine ring;
- n is 1, 2 or 3;
- 10 and to pharmaceutically acceptable acid addition salts thereof.

It has surprisingly been found that the compounds of general formula I are adenosine receptor ligands. Specifically, the compounds of the present invention have a good affinity to the A_{2A}-receptor and a high selectivity to the A₁- and A₃ receptors.

Adenosine modulates a wide range of physiological functions by interacting with
15 specific cell surface receptors. The potential of adenosine receptors as drug targets was first reviewed in 1982. Adenosine is related both structurally and metabolically to the bioactive nucleotides adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP) and cyclic adenosine monophosphate (cAMP); to the biochemical methylation agent S-adenosyl-L-methionine (SAM); and structurally to the coenzymes NAD,

FAD and coenzym A; and to RNA. Together adenosine and these related compounds are important in the regulation of many aspects of cellular metabolism and in the modulation of different central nervous system activities.

The receptors for adenosine have been classified as A₁, A_{2A}, A_{2B} and A₃ receptors, belonging to the family of G protein-coupled receptors. Activation of adenosine receptors by adenosine initiates signal transduction mechanism. These mechanisms are dependent on the receptor associated G protein. Each of the adenosine receptor subtypes has been classically characterised by the adenylate cyclase effector system, which utilises cAMP as a second messenger. The A₁ and A₃ receptors, coupled with G_i proteins inhibit adenylate cyclase, leading to a decrease in cellular cAMP levels, while A_{2A} and A_{2B} receptors couple to G_s proteins and activate adenylate cyclase, leading to an increase in cellular cAMP levels. It is known that the A₁ receptor system includes the activation of phospholipase C and modulation of both potassium and calcium ion channels. The A₃ subtype, in addition to its association with adenylate cyclase, also stimulates phospholipase C and so activates calcium ion channels.

The A₁ receptor (326-328 amino acids) was cloned from various species (canine, human, rat, dog, chick, bovine, guinea-pig) with 90-95 % sequence identity among the mammalian species. The A_{2A} receptor (409-412 amino acids) was cloned from canine, rat, human, guinea pig and mouse. The A_{2B} receptor (332 amino acids) was cloned from human and mouse with 45 % homology of human A_{2B} with human A₁ and A_{2A} receptors. The A₃ receptor (317-320 amino acids) was cloned from human, rat, dog, rabbit and sheep.

The A₁ and A_{2A} receptor subtypes are proposed to play complementary roles in adenosine's regulation of the energy supply. Adenosine, which is a metabolic product of ATP, diffuses from the cell and acts locally to activate adenosine receptors to decrease the oxygen demand (A₁) or increase the oxygen supply (A_{2A}) and so reinstate the balance of energy supply: demand within the tissue. The actions of both subtypes is to increase the amount of available oxygen to tissue and to protect cells against damage caused by a short term imbalance of oxygen. One of the important functions of endogenous adenosine is preventing damage during traumas such as hypoxia, ischaemia, hypotension and seizure activity.

Furthermore, it is known that the binding of the adenosine receptor agonist to mast cells expressing the rat A₃ receptor resulted in increased inositol triphosphate and intracellular calcium concentrations, which potentiated antigen induced secretion of inflammatory mediators. Therefore, the A₃ receptor plays a role in mediating asthmatic attacks and other allergic responses.

Adenosine is a neuromodulator, able to modulate many aspects of physiological brain function. Endogenous adenosine, a central link between energy metabolism and neuronal activity, varies according to behavioural state and (patho)physiological conditions. Under conditions of increased demand and decreased availability of energy

5 (such as hypoxia, hypoglycemia, and/or excessive neuronal activity), adenosine provides a powerful protective feedback mechanism. Interacting with adenosine receptors represents a promising target for therapeutic intervention in a number of neurological and psychiatric diseases such as epilepsy, sleep, movement disorders (Parkinson or Huntington's disease), Alzheimer's disease, depression, schizophrenia, or addiction. An increase in

10 neurotransmitter release follows traumas such as hypoxia, ischaemia and seizures. These neurotransmitters are ultimately responsible for neural degeneration and neural death, which causes brain damage or death of the individual. The adenosine A₁ agonists which mimic the central inhibitory effects of adenosine may therefore be useful as neuroprotective agents. Adenosine has been proposed as an endogenous anticonvulsant

15 agent, inhibiting glutamate release from excitatory neurons and inhibiting neuronal firing. Adenosine agonists therefore may be used as antiepileptic agents. Adenosine antagonists stimulate the activity of the CNS and have proven to be effective as cognition enhancers. Selective A_{2a} antagonists have therapeutic potential in the treatment of various forms of dementia, for example in Alzheimer's disease, and of neurodegenerative disorders, e.g.

20 stroke. Adenosine A_{2a} receptor antagonists modulate the activity of striatal GABAergic neurons and regulate smooth and well-coordinated movements, thus offering a potential therapy for Parkinsonian symptoms. Adenosine is also implicated in a number of physiological processes involved in sedation, hypnosis, schizophrenia, anxiety, pain, respiration, depression, and drug addiction (amphetamine, cocaine, opioids, ethanol,

25 nicotine, cannabinoids). Drugs acting at adenosine receptors therefore have therapeutic potential as sedatives, muscle relaxants, antipsychotics, anxiolytics, analgesics, respiratory stimulants, antidepressants, and to treat drug abuse. They may also be used in the treatment of ADHD (attention deficit hyper-activity disorder).

An important role for adenosine in the cardiovascular system is as a cardioprotective agent. Levels of endogenous adenosine increase in response to ischaemia and hypoxia, and protect cardiac tissue during and after trauma (preconditioning). By acting at the A₁ receptor, adenosine A₁ agonists may protect against the injury caused by myocardial ischemia and reperfusion. The modulating influence of A_{2a} receptors on adrenergic function may have implications for a variety of disorders such as coronary artery disease and heart failure. A_{2a} antagonists may be of therapeutic benefit in situations in which an enhanced antiadrenergic response is desirable, such as during acute myocardial ischemia. Selective antagonists at A_{2a} receptors may also enhance the effectiveness of adenosine in terminating supraventricular arrhythmias.

Adenosine modulates many aspects of renal function, including renin release, glomerular filtration rate and renal blood flow. Compounds which antagonise the renal affects of adenosine have potential as renal protective agents. Furthermore, adenosine A₃ and/or A_{2B} antagonists may be useful in the treatment of asthma and other allergic responses or and in the treatment of diabetes mellitus and obesity.

Numerous documents describe the current knowledge on adenosine receptors, for example the following publications:

Bioorganic & Medicinal Chemistry, 6, (1998), 619-641,
Bioorganic & Medicinal Chemistry, 6, (1998), 707-719,
10 J. Med. Chem., (1998), 41, 2835-2845,
J. Med. Chem., (1998), 41, 3186-3201,
J. Med. Chem., (1998), 41, 2126-2133,
J. Med. Chem., (1999), 42, 706-721,
J. Med. Chem., (1996), 39, 1164-1171,
15 Arch. Pharm. Med. Chem., 332, 39-41, (1999),
Am. J. Physiol., 276, H1113-1116, (1999) or
Naunyn Schmied, Arch. Pharmacol. 362, 375-381, (2000).

Objects of the present invention are the compounds of formula I per se, the use of compounds of formula I and their pharmaceutically acceptable salts for the manufacture of medicaments for the treatment of diseases, related to the adenosine A₂ receptor, their manufacture, medicaments based on a compound in accordance with the invention and their production as well as the use of compounds of formula I in the control or prevention of illnesses based on the modulation of the adenosine system, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, neuroprotection, schizophrenia, anxiety, pain, respiration deficits, depression, drug addiction, such as amphetamine, cocaine, opioids, ethanol, nicotine, cannabinoids, or against asthma, allergic responses, hypoxia, ischaemia, seizure and substance abuse. Furthermore, compounds of the present invention may be useful as sedatives, muscle relaxants, antipsychotics, antiepileptics, anticonvulsants and cardioprotective agents for disorders such as coronary artery disease and heart failure. The most preferred indications in accordance with the present invention are those, which base on the A_{2A} receptor antagonistic activity and which include disorders of the central nervous system, for example the treatment or prevention of Alzheimer's disease, certain depressive disorders, drug addiction, neuroprotection and Parkinson's disease as well as ADHD.

As used herein, the term "lower alkyl" denotes a saturated straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms, for example, methyl, ethyl, propyl,

isopropyl, n-butyl, i-butyl, 2-butyl, t-butyl and the like. Preferred lower alkyl groups are groups with 1 - 4 carbon atoms.

The term "halogen" denotes chlorine, iodine, fluorine and bromine.

5 The term "lower alkoxy" denotes a group wherein the alkyl residues is as defined above, and which is attached via an oxygen atom.

The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid and the like.

10 Preferred compounds of the present application are compounds of formula I, wherein R² is -(CH₂)_n-O-lower alkyl and R¹ is hydrogen or lower alkyl, for example the following compounds:

4-[(2-methoxy-acetylamino)-methyl]-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide or

15 4-[(methoxyacetyl-methyl-amino)-methyl]-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide.

Further preferred are compounds, wherein R² is C₃₋₆-cycloalkyl and R¹ is hydrogen or lower alkyl, for example the following compounds:

20 4-[(cyclopropanecarbonyl-amino)-methyl]-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide,

4-[(cyclobutanecarbonyl-amino)-methyl]-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide,

4-[(cyclopropanecarbonyl-methyl-amino)-methyl]-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide or

25 4-[(cyclobutanecarbonyl-methyl-amino)-methyl]-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide.

A further preferred group of compounds are those, wherein R² is lower alkyl and R¹ is hydrogen or lower alkyl, for example the following compounds:

30 N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-[(methyl-propionyl-amino)-methyl]-benzamide,

N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-(propionylamino-methyl)-benzamide,

4-[(acetyl-methyl-amino)-methyl]-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide,

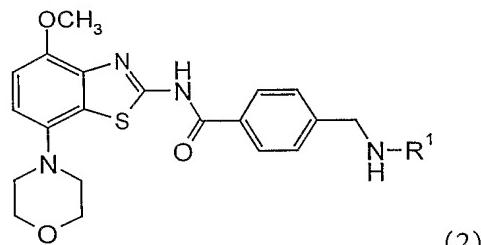
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4-(acetyl-amino-methyl)-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide
or
4-[(ethyl-propionyl-amino)-methyl]-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide.

5 Further preferred compounds are those, wherein R² is the group -(CH₂)_n-NR'₂ and
R¹ is lower alkyl,
4-[(dimethylaminoacetyl-methyl-amino)-methyl]-N-(4-methoxy-7-morpholin-4-yl-
benzothiazol-2-yl)-benzamide
N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-{{[methyl-(pyrrolidin-1-yl-acetyl)-
10 amino]-methyl}-benzamide

The present compounds of formula I and their pharmaceutically acceptable salts can
be prepared by methods known in the art, for example, by processes described below,
which process comprises

a) reacting a compound of formula

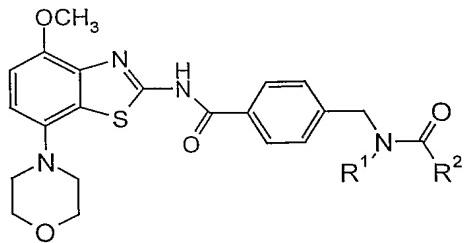


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with a compound of formula



to a compound of formula



20 wherein R¹ and R² are as defined above, and,

if desired, converting the compounds obtained into pharmaceutically acceptable acid
addition salts.

- 7 -

The compounds of formula I may be prepared in accordance with process variant a) and with the following scheme 1:

In scheme 1 the preparation of the starting material (4) and intermediates (5), (6), (7), (8) and (9) have been described in more detail in EP 00113219.0.

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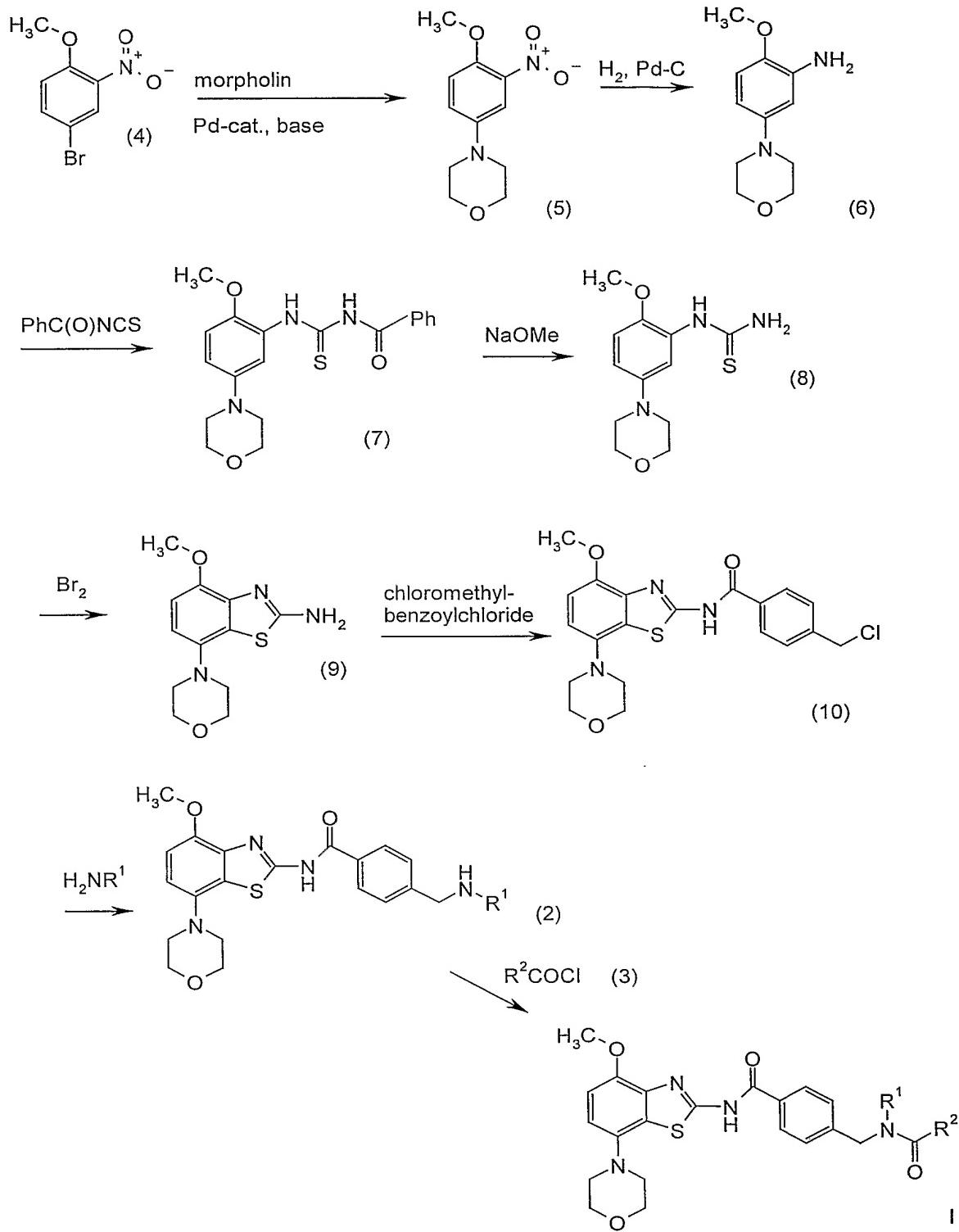
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- 8 -

Scheme 1



wherein R¹ and R² are defined above.

The compounds of formula I are prepared as follows:

A compound of formula (2), for example *N*-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-aminomethyl-benzamide, dissolved in dichloromethane is treated with pyridine and with a compound of formula (3), for example methoxy-acetyl chloride or cyclopropanecarbonyl chloride, and stirred at ambient temperature for about 15 h.

- 5 Saturated aqueous sodium carbonate is added, the phases are separated and the aqueous solution extracted. The combined organic phases are dried, filtered and evaporated to dryness and the corresponding compound of formula I is obtained.

Isolation and purification of the compounds

Isolation and purification of the compounds and intermediates described herein can be effected, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography, thick-layer chromatography, preparative low or high-pressure liquid chromatography or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures can be had by reference to the Preparations and Examples herein below. However, other equivalent separation or isolation procedures could, of course, also be used.

Salts of compounds of formula I

The compounds of formula I may be basic, for example in cases where the residue R² contains a basic group such as an aliphatic or aromatic amine moiety. In such cases the compounds of formula I may be converted to a corresponding acid addition salt.

The conversion is accomplished by treatment with at least a stoichiometric amount of an appropriate acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. Typically, the free base is dissolved in an inert organic solvent such as diethyl ether, ethyl acetate, chloroform, ethanol or methanol and the like, and the acid added in a similar solvent. The temperature is maintained between 0 °C and 50 °C. The resulting salt precipitates spontaneously or may be brought out of solution with a less polar solvent.

The acid addition salts of the basic compounds of formula I may be converted to the corresponding free bases by treatment with at least a stoichiometric equivalent of a suitable base such as sodium or potassium hydroxide, potassium carbonate, sodium bicarbonate, ammonia, and the like.

The compounds of formula I and their pharmaceutically usable addition salts possess valuable pharmacological properties. Specifically, it has been found that the compounds of the present invention are adenosine receptor ligands and possess a high affinity towards the adenosine A_{2A} receptor.

5 The compounds were investigated in accordance with the test given hereinafter.

Human adenosine A_{2A} receptor

The human adenosine A_{2A} receptor was recombinantly expressed in chinese hamster ovary (CHO) cells using the semliki forest virus expression system. Cells were harvested, washed twice by centrifugation, homogenised and again washed by centrifugation. The 10 final washed membrane pellet was suspended in a Tris (50 mM) buffer containing 120 mM NaCl, 5 mM KCl, 2 mM CaCl₂ and 10 mM MgCl₂ (pH 7.4) (buffer A). The [³H]-SCH-58261 (Dionisotti et al., 1997, Br J Pharmacol 121, 353; 1nM) binding assay was carried out in 96-well plates in the presence of 2.5 µg of membrane protein, 0.5 mg of Ysi-poly-l-lysine SPA beads and 0.1 U adenosine deaminase in a final volume of 200 µl of buffer A. Non- 15 specific binding was defined using xanthine amine congener (XAC; 2 µM). Compounds were tested at 10 concentrations from 10 µM - 0.3 nM. All assays were conducted in duplicate and repeated at least two times. Assay plates were incubated for 1hour at room temperature before centrifugation and then bound ligand determined using a Packard Topcount scintillation counter. IC₅₀ values were calculated using a non-linear curve fitting 20 program and Ki values calculated using the Cheng-Prussoff equation.

The preferred compounds show a pKi > 8.8.

Example No.	hA ₂ (pKi)
1	9.1
2	8.9
4	9.2
5	9.1
6	9.2
7	9.0
9	9.0

10	9.0
11	9.3
12	9.1
14	8.9
15	8.9
19	8.8

The compounds of formula I and the pharmaceutically acceptable salts of the compounds of formula I can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form 5 of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions.

The compounds of formula I can be processed with pharmaceutically inert, inorganic 10 or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acids or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the 15 production of solutions and syrups are, for example, water, polyols, glycerol, vegetable oil and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

The pharmaceutical preparations can, moreover, contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying 20 the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

Medicaments containing a compound of formula I or a pharmaceutically acceptable salt thereof and a therapeutically inert carrier are also an object of the present invention, as is a process for their production, which comprises bringing one or more compounds of 25 formula I and/or pharmaceutically acceptable acid addition salts and, if desired, one or

- 12 -

more other therapeutically valuable substances into a galenical administration form together with one or more therapeutically inert carriers.

In accordance with the invention compounds of formula I as well as their pharmaceutically acceptable salts are useful in the control or prevention of illnesses based 5 on the adenosine receptor antagonistic activity, such as Alzheimer's disease, Parkinson's disease, neuroprotection, schizophrenia, anxiety, pain, respiration deficits, depression, asthma, allergic responses, hypoxia, ischaemia, seizure and substance abuse. Furthermore, compounds of the present invention may be useful as sedatives, muscle relaxants, antipsychotics, antiepileptics, anticonvulsants and cardioprotective agents and for the 10 production of corresponding medicaments.

The most preferred indications in accordance with the present invention are those, which include disorders of the central nervous system, for example the treatment or prevention of certain depressive disorders, neuroprotection and Parkinson's disease.

The dosage can vary within wide limits and will, of course, have to be adjusted to the 15 individual requirements in each particular case. In the case of oral administration the dosage for adults can vary from about 0.01 mg to about 1000 mg per day of a compound of general formula I or of the corresponding amount of a pharmaceutically acceptable salt thereof. The daily dosage may be administered as single dose or in divided doses and, in addition, the upper limit can also be exceeded when this is found to be indicated.

20

Tablet Formulation (Wet Granulation)

<u>Item</u>	<u>Ingredients</u>	<u>mg/tablet</u>			
		5 mg	25 mg	100 mg	500 mg
1.	Compound of formula I	5	25	100	500
2.	Lactose Anhydrous DTG	125	105	30	150
25	3.	Sta-Rx 1500	6	6	30
	4.	Microcrystalline Cellulose	30	30	150
	5.	Magnesium Stearate	1	1	1
	Total	167	167	167	831

30

Manufacturing Procedure

1. Mix items 1, 2, 3 and 4 and granulate with purified water.
2. Dry the granules at 50°C.
3. Pass the granules through suitable milling equipment.
- 5 4. Add item 5 and mix for three minutes; compress on a suitable press.

Capsule Formulation

<u>Item</u>	<u>Ingredients</u>	<u>mg/capsule</u>			
		5 mg	25 mg	100 mg	500 mg
1.	Compound of formula I	5	25	100	500
10	2. Hydrous Lactose	159	123	148	---
	3. Corn Starch	25	35	40	70
	4. Talc	10	15	10	25
	5. Magnesium Stearate	1	2	2	5
	Total	200	200	300	600

Manufacturing Procedure

1. Mix items 1, 2 and 3 in a suitable mixer for 30 minutes.
2. Add items 4 and 5 and mix for 3 minutes.
3. Fill into a suitable capsule.

Example 1

20 4-[(2-Methoxy-acetylamino)-methyl]-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide

N-(4-Methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-aminomethyl-benzamide (100 mg, 0.24 mmol), dissolved in dichloromethane (5 ml) is treated with pyridine (29 µl, 0.36 mmol) and methoxy-acetyl chloride (24 µl, 0.32 mmol) and stirred at ambient 25 temperature for 15 h. Saturated aqueous sodium carbonate (6 ml) is added, the phases are separated and the aqueous solution extracted twice with each 5 ml dichloromethane. The combined organic phases are dried over sodium sulphate, filtered and evaporated to dryness. Flash chromatography (silica, eluent: dichloromethane containing 3 % methanol) afforded the title compound as white crystals (71 % yield). MS: m/e=471(M+H⁺).

Following the general method of example 1 the compounds of examples 2 to 16 were prepared.

Example 2

- 4-[(Methoxyacetyl-methyl-amino)-methyl]-N-(4-methoxy-7-morpholin-4-yl-
5 benzothiazol-2-yl)-benzamide

Using *N*-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-methylaminomethyl-benzamide and methoxy-acetyl chloride, the title compound was prepared as yellow solid (83 % yield). MS: m/e=485(M+H⁺).

Example 3

- 10 *N*-(4-Methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-{[(3-methoxy-propionyl)-methyl-amino]-methyl}-benzamide

Using *N*-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-methylaminomethyl-benzamide and 3-methoxy-propionyl chloride, the title compound was prepared as light yellow crystals (46 % yield). MS: m/e=499(M+H⁺).

- 15 Example 4

4-[(Cyclopropanecarbonyl-methyl-amino)-methyl]-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide

- 20 Using *N*-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-methylaminomethyl-benzamide and cyclopropanecarbonyl chloride, the title compound was prepared as light yellow crystals (82 % yield). MS: m/e=481(M+H⁺).

Example 5

4-[(Cyclobutanecarbonyl-methyl-amino)-methyl]-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide

- 25 Using *N*-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-methylaminomethyl-benzamide and cyclobutanecarbonyl chloride, the title compound was prepared as light yellow crystals (59 % yield). MS: m/e=495(M+H⁺).

Example 6

N-(4-Methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-[(methyl-propionyl-amino)-methyl]-benzamide

Using *N*-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-methylaminomethyl-benzamide and propionyl chloride, the title compound was prepared as white crystals (59 % yield). MS: m/e=469(M+H⁺).

Example 7

- 5 *N*-(4-Methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-(propionylamino-methyl)-benzamide

Using *N*-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-aminomethyl-benzamide and propionyl chloride, the title compound was prepared as off-white crystals (34 % yield). MS: m/e=455(M+H⁺).

10

Example 8

N-(4-Methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-[(3-methoxy-propionylamino)-methyl]-benzamide

- 15 Using *N*-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-aminomethyl-benzamide and 3-methoxy-propionyl chloride, the title compound was prepared as white crystals (44 % yield). MS: m/e=485(M+H⁺).

Example 9

4-[(Cyclopropanecarbonyl-amino)-methyl]-*N*-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide

- 20 Using *N*-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-aminomethyl-benzamide and cyclopropanecarbonyl chloride, the title compound was prepared as light-yellow crystals (64 % yield). MS: m/e=467(M+H⁺).

Example 10

4-[(Acetyl-methyl-amino)-methyl]-*N*-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide

- 25 Using *N*-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-methylaminomethyl-benzamide and acetyl chloride, the title compound was prepared as white crystals (77 % yield). MS: m/e=455(M+H⁺).

Example 11

4-[(Cyclobutanecarbonyl-amino)-methyl]-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide

Using *N*-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-aminomethyl-benzamide and cyclobutanecarbonyl chloride, the title compound was prepared as off-white crystals (52 % yield). MS: m/e=481(M+H⁺).

Example 12

4-(Acetylamino-methyl)-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide

Using *N*-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-aminomethyl-benzamide and acetyl chloride, the title compound was prepared as white crystals (17 % yield). MS: m/e=441(M+H⁺).

Example 13

4-[(Ethyl-methoxyacetyl-amino)-methyl]-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide

Using *N*-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-ethylaminomethyl-benzamide and methoxy-acetyl chloride, the title compound was prepared as white solid (33 % yield). MS: m/e=499(M+H⁺).

Example 14

4-[(Ethyl-propionyl-amino)-methyl]-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide

Using *N*-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-ethylaminomethyl-benzamide and propionyl chloride, the title compound was prepared as white solid (47 % yield). MS: m/e=483(M+H⁺).

Example 15

4-[(Dimethylaminoacetyl-methyl-amino)-methyl]-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide

Using *N*-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-methylaminomethyl-benzamide and dimethylamino-acetyl chloride, the title compound was prepared as light yellow crystals (46 % yield). MS: m/e=498(M+H⁺).

Example 16 (intermediate)**4-[(Chloroacetyl-methyl-amino)-methyl]-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide**

Using *N*-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-methylaminomethyl-benzamide and chloroacetyl chloride, the title compound was prepared as yellow foam (51 % yield). MS: m/e=489 (M+H⁺).

Example 17***N*-(4-Methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-(2-oxo-pyrrolidin-1-yl-methyl)-benzamide**

Sodium hydride (48 mg, 0.48 mmol, 60 % in mineral oil) are suspended in dimethyl formamide (2.0 ml) and at 0°C treated with pyrrolidin-2-one. After stirring for 1 h at 50 °C, *N*-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-chloromethyl-benzamide (200 mg, 0.48 mmol) was added and the solution stirred for 5 h at 80 °C. Removal of the volatile components in vacuo and flash chromatography (silica, eluent dichloromethane/methanol 19:1) afforded the title compound as off-white crystals (86 % yield). MS: m/e=467(M+H⁺).

Example 18**4-[[{[(2-Methoxy-ethyl)-methyl-amino]-acetyl}-methyl-amino]-methyl]-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide**

4-[(Chloroacetyl-methyl-amino)-methyl]-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide (100 mg, 205 mmol) are dissolved in N-(2-methoxyethyl)-methylamine (1.8 ml, 21 mmol) and the mixture stirred for 2h at 55 °C. Saturated aqueous sodium hydrogen carbonate is added (50 ml) and dichloromethane (50 ml) are added, the phases are separated and the aqueous phase extracted twice with 50 ml dichloromethane. The combined organic layers are dried with magnesium sulfate and evaporated. Flash chromatography (silica, dichloromethane containing 5 % methanol) afforded the title compound as white crystals (74 % yield), mp 171-173 °C. MS: m/e=542 (M+H⁺).

Following the general method of example 18 the compound of example 19 was prepared.

- 18 -

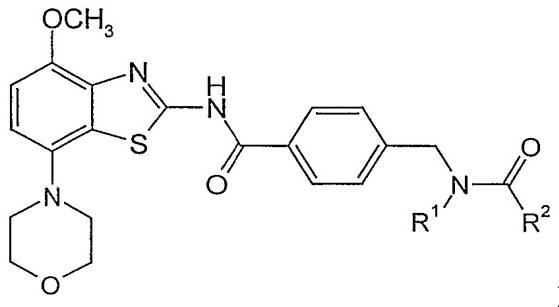
Example 19

N-(4-Methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-{[methyl-(pyrrolidin-1-yl-acetyl)-amino]-methyl}-benzamide

Using 4-[(Chloroacetyl-methyl-amino)-methyl]-N-(4-methoxy-7-morpholin-4-yl-
5 benzothiazol-2-yl)-benzamide and pyrrolidine the title compound was obtained as white
crystals (61 % yield), mp 114-116°C). MS: m/e=524 (M+H+).

Claims

Compounds of the general formula



wherein

- 5 R¹ is hydrogen or lower alkyl;
- R² is lower alkyl, -(CH₂)_n-O-lower alkyl, -C₃₋₆-cycloalkyl or -(CH₂)_n-NR'₂;
- R' is hydrogen, lower alkyl or -(CH₂)_n-O-lower alkyl, independently from each other
for R'₂, or R'₂ may form together with the N atom a pyrrolidine ring;

n is 1, 2 or 3;

10 and pharmaceutically acceptable acid addition salts thereof.

2. Compounds of formula I in accordance with claim 1, wherein R² is
-(CH₂)_n-O-lower alkyl and R¹ is hydrogen or lower alkyl.

15 3. Compounds of formula I in accordance with claim 2, wherein the compound is
4-[(2-methoxy-acetylamino)-methyl]-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide or
4-[(methoxyacetyl-methyl-amino)-methyl]-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide.

20 4. Compounds in accordance with claim 1, wherein R² is C₃₋₆-cycloalkyl and R¹ is
hydrogen or lower alkyl.

25 5. Compounds in accordance with claim 4, wherein the compound is
4-[(cyclopropanecarbonyl-amino)-methyl]-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide,
4-[(cyclobutanecarbonyl-amino)-methyl]-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide,

4-[(cyclopropanecarbonyl-methyl-amino)-methyl]-*N*-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide or

4-[(cyclobutanecarbonyl-methyl-amino)-methyl]-*N*-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide.

5 6. Compounds in accordance with claim 1, wherein R² is lower alkyl and R¹ is hydrogen or lower alkyl.

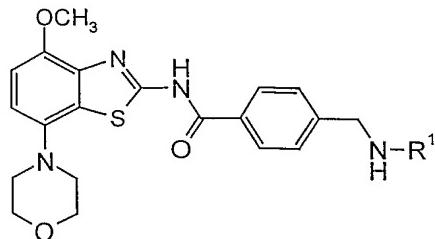
7. Compounds in accordance with claim 6, wherein the compound is
 N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-[(methyl-propionyl-amino)-
 10 methyl]-benzamide,
 N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-(propionylamino-methyl)-
 benzamide,
 4-[(acetyl-methyl-amino)-methyl]-*N*-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-
 benzamide,
 15 4-(acetylamino-methyl)-*N*-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-benzamide
 or
 4-[(ethyl-propionyl-amino)-methyl]-*N*-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-
 yl)-benzamide.

8. Compounds in accordance with claim 1, wherein R² is the group -(CH₂)_n-NR'₂
 20 and R¹ is lower alkyl.

9. Compounds in accordance with claim 8, wherein the compound is
 4-[(dimethylaminoacetyl-methyl-amino)-methyl]-*N*-(4-methoxy-7-morpholin-4-yl-
 benzothiazol-2-yl)-benzamide
 N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-4-{[methyl-(pyrrolidin-1-yl-acetyl)-
 25 amino]-methyl}-benzamide

10. A process for preparing a compound of formula I as defined in claims 1 - 9, which
 process comprises

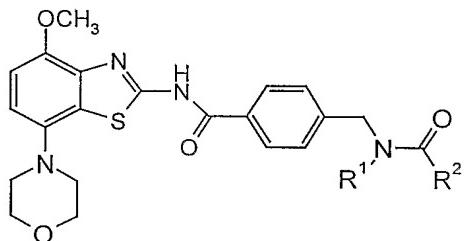
a) reacting a compound of formula



with a compound of formula



to a compound of formula



5 wherein R¹ and R² are as defined in claim 1, and,

if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

11. A compound according to any one of claims 1 to 9, whenever prepared by a process as claimed in claim 10 or by an equivalent method.

10 12. A medicament containing one or more compounds as claimed in any one of claims 1 to 9 and pharmaceutically acceptable excipients.

13. A medicament according to claim 12 for the treatment of diseases related to the adenosine receptor.

14. The use of a compound in any one of claims 1 to 9 for the treatment of diseases.

15 15. The use of a compound in any one of claims 1 to 9 for the manufacture of corresponding medicaments for the treatment of diseases related to the adenosine A_{2A} receptor.

16. The invention as hereinbefore described.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/13046

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/428 C07D277/82

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 01 97786 A (HOFFMANN LA ROCHE) 27 December 2001 (2001-12-27) cited in the application see the whole document, especially definitions of R and examples ---	1-16
A	EP 0 295 656 A (EISAI CO LTD) 21 December 1988 (1988-12-21) the whole document ---	1-16 --/--

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BARALDI P G ET AL: "COMPARATIVE MOLECULAR FIELD ANALYSIS (COMFA) OF A SERIES OF SELECTIVE ADENOSINE RECEPTOR A2A ANTAGONIST" DRUG DEVELOPMENT RESEARCH, NEW YORK, NY, US, vol. 46, no. 2, 1999, pages 126-133, XP008004853 ISSN: 0272-4391 the whole document ----	1-16
A	EP 0 343 893 A (PFIZER) 29 November 1989 (1989-11-29) the whole document ----	1-16
A	EP 0 604 657 A (OTSUKA PHARMA CO LTD) 6 July 1994 (1994-07-06) the whole document -----	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/13046

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 0197786	A	27-12-2001	AU WO US	8181701 A 0197786 A2 2002045615 A1		02-01-2002 27-12-2001 18-04-2002
EP 0295656	A	21-12-1988	AT AU AU CA CN DD DE DE DK EP ES FI GR HU JP JP KR NO NZ PH PT SU US ZA	82276 T 610186 B2 1769988 A 1322369 A1 1030757 A 282686 A5 3875809 D1 3875809 T2 328888 A 0295656 A1 2045017 T3 882692 A ,B, 3006207 T3 47554 A2 1079162 A 2793195 B2 9105709 B1 882627 A ,B, 224946 A 26553 A 87747 A ,B 1731051 A3 4929623 A 8804277 A		15-11-1992 16-05-1991 22-12-1988 21-09-1993 01-02-1989 19-09-1990 17-12-1992 15-04-1993 18-12-1988 21-12-1988 16-01-1994 18-12-1988 21-06-1993 28-03-1989 24-03-1989 03-09-1998 02-08-1991 19-12-1988 26-07-1990 19-08-1992 01-07-1988 30-04-1992 29-05-1990 29-03-1989
EP 0343893	A	29-11-1989	AT AU AU CA CN DD DE DE DK EP ES FI GR HU IE JP JP KR MX NO NZ PL PT SU US YU ZA	79114 T 601905 B2 3509889 A 1328871 A1 1037898 A ,B 283815 A5 68902358 D1 68902358 T2 249389 A 0343893 A1 2043012 T3 892498 A 3005844 T3 51606 A2 891667 L 2017181 A 6078331 B 9106864 B1 16158 A ,B 892059 A ,B, 229234 A 279613 A1 90622 A ,B 1681728 A3 4970318 A 105989 A1 8903862 A		15-08-1992 20-09-1990 30-11-1989 26-04-1994 13-12-1989 24-10-1990 10-09-1992 10-12-1992 27-11-1989 29-11-1989 16-12-1993 25-11-1989 07-06-1993 28-05-1990 24-11-1989 22-01-1990 05-10-1994 09-09-1991 01-06-1993 27-11-1989 26-09-1990 27-11-1989 30-11-1989 30-09-1991 13-11-1990 31-08-1990 30-01-1991
EP 0604657	A	06-07-1994	AT	188704 T		15-01-2000

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/13046

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 0604657	A	AU	653681 B2	06-10-1994
		DE	69327572 D1	17-02-2000
		DE	69327572 T2	21-06-2000
		DK	604657 T3	17-04-2000
		EP	0604657 A1	06-07-1994
		KR	185225 B1	15-05-1999
		US	5376665 A	27-12-1994
		AU	4088793 A	13-12-1993
		CA	2113561 A1	25-11-1993
		ES	2140456 T3	01-03-2000
		WO	9323409 A1	25-11-1993
		JP	2759228 B2	28-05-1998
		PT	604657 T	28-04-2000